

(FILE 'HOME' ENTERED AT 17:30:39 ON 18 FEB 2004)

FILE 'USPATFULL' ENTERED AT 17:31:23 ON 18 FEB 2004

L1 1993 S (SODIUM (2A) CHANNEL)
L2 41954 S SUBUNIT OR SUB UNIT
L3 923 S L1 AND L2
L4 150 S L3 AND (SS1 OR SS2 OR S5 OR S6)
L5 1562589 S INHIBIT? OR BLOCK? OR ANTAGON?
L6 149 S L4 AND L5

FILE 'CAPLUS, USPATFULL' ENTERED AT 17:33:06 ON 18 FEB 2004

L7 39 FILE CAPLUS
L8 149 FILE USPATFULL
TOTAL FOR ALL FILES
L9 188 S L6
L10 24 FILE CAPLUS
L11 31 FILE USPATFULL
TOTAL FOR ALL FILES
L12 55 S L7 NOT ?TOXIN?
L13 1066 FILE CAPLUS
L14 401 FILE USPATFULL
TOTAL FOR ALL FILES
L15 1467 S L1 (1S) L2
L16 20 FILE CAPLUS
L17 48 FILE USPATFULL
TOTAL FOR ALL FILES
L18 68 S L15 (1S) (SS1 OR SS2 OR S5 OR S6)
L19 8 FILE CAPLUS
L20 21 FILE USPATFULL
TOTAL FOR ALL FILES
L21 29 S L18 (1S) L5
L22 0 FILE CAPLUS
L23 9 FILE USPATFULL
TOTAL FOR ALL FILES
L24 9 S L21 AND L1/CLM
SAVE ALL L10062483/L
SAVE L24 A10062483/A
L25 1492 FILE CAPLUS
L26 2366 FILE USPATFULL
TOTAL FOR ALL FILES
L27 3858 S ?TOXIN? AND (OPIOID? OR OPIATE? OR MORPHIN OR MORPHAN)
L28 1490 FILE CAPLUS
L29 2362 FILE USPATFULL
TOTAL FOR ALL FILES
L30 3852 S ?TOXIN? AND (OPIOID? OR OPIATE?)
L31 896 FILE CAPLUS
L32 871 FILE USPATFULL
TOTAL FOR ALL FILES
L33 1767 S ?TOXIN? (1S) (OPIOID? OR OPIATE?)
L34 58 FILE CAPLUS
L35 196 FILE USPATFULL
TOTAL FOR ALL FILES
L36 254 S L33 (1S) (PAIN OR ANALGESIC)
L37 31 FILE CAPLUS
L38 178 FILE USPATFULL
TOTAL FOR ALL FILES
L39 209 S L36 AND (POTENTIAT? OR ENHANC? OR IMPROV? OR INCREAS? OR SYNE
L40 19 FILE CAPLUS
L41 78 FILE USPATFULL
TOTAL FOR ALL FILES
L42 97 S L36 (1S) (POTENTIAT? OR ENHANC? OR IMPROV? OR INCREAS? OR SYN
SAVE ALL L10062483/L
L43 2829 FILE CAPLUS

L44 383 FILE USPATFULL
 TOTAL FOR ALL FILES
 L45 3212 S CONOTOXIN
 L46 42317 FILE CAPLUS
 L47 6760 FILE USPATFULL
 TOTAL FOR ALL FILES
 L48 49077 S (OPIOID? OR OPIATE? OR MORPHIN OR MORPHAN)
 L49 3413 FILE CAPLUS
 L50 2284 FILE USPATFULL
 TOTAL FOR ALL FILES
 L51 5697 S L48 (1S) (PAIN OR ANLGES?)
 L52 2 FILE CAPLUS
 L53 13 FILE USPATFULL
 TOTAL FOR ALL FILES
 L54 15 S L51 (1S) L45
 L55 0 FILE CAPLUS
 L56 13 FILE USPATFULL
 TOTAL FOR ALL FILES
 L57 13 S L54 AND (CONCURRENT? OR CO-ADMINIST? OR (COADMINIST?) OR COMB
 SAVE ALL L10062483/L
 SAVE L57 B10062483/A

=> s (sodium (2a) channel)
L1 11123 FILE EMBASE
L2 11300 FILE CAPLUS
L3 1993 FILE USPATFULL

TOTAL FOR ALL FILES
L4 24416 (SODIUM (2A) CHANNEL)

=> s subunit and (ss1 or ss2 or s5 or s6)
L5 549 FILE EMBASE
L6 1014 FILE CAPLUS
L7 1230 FILE USPATFULL

TOTAL FOR ALL FILES
L8 2793 SUBUNIT AND (SS1 OR SS2 OR S5 OR S6)

=> s l8 and l4
L9 54 FILE EMBASE
L10 79 FILE CAPLUS
L11 149 FILE USPATFULL

TOTAL FOR ALL FILES
L12 282 L8 AND L4

=> s l12 not toxin
L13 48 FILE EMBASE
L14 70 FILE CAPLUS
L15 52 FILE USPATFULL

TOTAL FOR ALL FILES
L16 170 L12 NOT TOXIN

=> d l13 1-48 all

(FILE 'HOME' ENTERED AT 17:30:39 ON 18 FEB 2004)

FILE 'USPATFULL' ENTERED AT 17:31:23 ON 18 FEB 2004

L1 1993 S (SODIUM (2A) CHANNEL)
L2 41954 S SUBUNIT OR SUB UNIT
L3 923 S L1 AND L2
L4 150 S L3 AND (SS1 OR SS2 OR S5 OR S6)
L5 1562589 S INHIBIT? OR BLOCK? OR ANTAGON?
L6 149 S L4 AND L5

FILE 'CAPLUS, USPATFULL' ENTERED AT 17:33:06 ON 18 FEB 2004

L7 39 FILE CAPLUS
L8 149 FILE USPATFULL
TOTAL FOR ALL FILES
L9 188 S L6
L10 24 FILE CAPLUS
L11 31 FILE USPATFULL
TOTAL FOR ALL FILES
L12 55 S L7 NOT ?TOXIN?
L13 1066 FILE CAPLUS
L14 401 FILE USPATFULL
TOTAL FOR ALL FILES
L15 1467 S L1 (1S) L2
L16 20 FILE CAPLUS
L17 48 FILE USPATFULL
TOTAL FOR ALL FILES
L18 68 S L15 (1S) (SS1 OR SS2 OR S5 OR S6)
L19 8 FILE CAPLUS
L20 21 FILE USPATFULL
TOTAL FOR ALL FILES
L21 29 S L18 (1S) L5
L22 0 FILE CAPLUS
L23 9 FILE USPATFULL
TOTAL FOR ALL FILES
L24 9 S L21 AND L1/CLM

=> save all

ENTER NAME OR (END):l10062483/1

L# LIST L1-L24 HAS BEEN SAVED AS 'L10062483/L'

=> save l24

ENTER NAME OR (END):a10062483/a

ANSWER SET L24 HAS BEEN SAVED AS 'A10062483/A'

L57 ANSWER 12 OF 13 USPATFULL on STN

DETD Shown in FIG. 15 are the results of experiments in which the effects of a sub-maximal dose of morphine were compared to those of the **combination** of a sub-maximal dose of morphine and a 0.5 µg (intrathecal) dose of SNX-185 in the Rat Tail-Flick Test. Intrathecal administration of SNX-185 enhanced the effects of a sub-maximal dose of morphine (FIG. 15) in this assay at all time points, and significantly at 45 min. after administration of compound.

DETD Analgesic potency of conopeptides can also be tested in animal models of neuropathic or neurogenic **pain**. One such model resembles the human condition termed causalgia or reflex sympathetic dystrophy (RSD) secondary to injury of a peripheral nerve. This condition is characterized by hyperesthesia (enhanced sensitivity to a natural stimulus), hyperalgesia (abnormal sensitivity to **pain**), allodynia (widespread tenderness, characterized by hypersensitivity to tactile stimuli), and spontaneous burning **pain**. In humans, neuropathic **pain** tends to be chronic and may be debilitating. This type of **pain** is generally considered to be non-responsive or only partially responsive to conventional **opioid** analgesic regimens (Jadad). In accordance with the invention, analgesic omega **conotoxin** peptides are effective in providing relief of neuropathic **pain**, as described below.

DETD Each BOC-AA-OH (2.4 mmol) was dissolved in 5 ml CH₂Cl₂ and cooled to 0° C. The volume of DCM used for BOC-Leu-OH (dried in vacuo) was 12 ml, and the BOC-Leu-OH solution was not cooled. 2 ml 0.6M DCCI in DCM was added and the **mixture** stirred at 0° C. for 15 min. For BOC-Leu-OH, the **mixture** was also cooled after this addition. Precipitation of N,N-dicyclohexylurea was completed by storage at -20° C. for 1.5 hour, after which the precipitate was filtered and washed with ethyl ether (5 ml). The filtrate was evaporated to remove solvents and the product was crystallized in the solvent system given in the Table below. Residual amounts of DCM can affect the exact conditions for crystallization. Recrystallization was performed by dissolving in DCM, evaporating most of the solvent, and recrystallizing from the appropriate solvent.

DETD For BOC-Arg(tosyl)-OH, the following **mixture** was prepared: 1.87 BOC-Arg(tosyl)-OH, 0.57 g 1-hydroxybenzotriazole, 15 ml DMF, stirred to dissolve, cooled to 4° C., added 0.52 ml diisopropylcarbodiimide, and split in half for steps 9 and 13. For this coupling, the protocol was modified as follows: step 8 was 3 times DCM wash and 2 times DMF wash; step 9 was for 10 min; step 11 was for 10 min; step 13 was for 10 min; step 14 was 0.4 mmol IPM in 4 ml DMF for 10 min; step 15 was for 10 min; step 16 was 1 times DMF wash and 1 time DCM wash. Reaction **mixtures** in steps 9, 10, 13, 14 and 18 were not drained.

DETD The **mixture** for a third coupling for incorporating the Arg-10 residue consisted of 1.00 g BOC-Arg(tosyl)-OH, 1 ml DMF, 5 ml DCM, stirred to dissolve, and cooled to 4° C. to which is then added 1.67ml 0.6M DCCI in DCM.

DETD A **mixture** of protected peptide resin (1.32 g), 2-mercaptopyridine (0.50 g), p-cresol (2.6 g), and liquid hydrogen fluoride (HF) (25 ml) was stirred at 0° C. for 80 min. The liquid HF was evaporated with a rapid stream of nitrogen gas, first below 0° C., then at 24° C. The **mixture** was stirred in ethyl acetate (25 ml) until a finely divided solid was obtained. The solid was filtered, washed with ethyl acetate, and air dried to yield 1.09 g. This solid was stirred in 50% aqueous acetic acid (10 ml) to dissolve the peptide material, filtered, and washed with 20 ml water. The filtrate was freeze-dried to yield 450 mg of fluffy powder.

DETD A sample (300 mg) of the fluffy powder was dissolved in 30 ml of 0.05M ammonium bicarbonate, 10 mM dithiothreitol (DTT), and 2M guanidine hydrochloride. The solution, which had a pH of 6.7, was allowed to stand at 24° C. for 2 hr, then diluted with 120 ml of water and stirred

for 20 hr at 24° C. DTT (25 mg) was added and the solution allowed to stand at 24° C. for 80 min. The **mixture** was then stirred at 4° C. for 3 days.

DETD 1. The lyophilized crude linear peptide was dissolved in 3M guanidine hydrochloride and 1.2M ammonium acetate solution to yield a concentration of approximately 12 mg peptide/ml. DTT was added to a ratio of 15 mg DTT per 100 mg peptide, and the **mixture** was stirred at room temperature for 1 hour. The solution was diluted 6-fold with distilled water, and stirred at 4° C. for 3-5 days. The progress of peptide oxidation was monitored by HPLC. The endpoint of the oxidation process was the complete disappearance of free thiols, determined by Ellman reaction.

DETD 2. The lyophilized crude linear peptide was dissolved in 3M guanidine hydrochloride and 0.3M potassium phosphate solution to yield a concentration of approximately 12 mg peptide/ml. After addition of 40 mg cysteine and 15 mg DTT per 100 mg peptide, the pH of the solution was adjusted to 8.0-8.1 with potassium hydroxide solution. The **mixture** was stirred at room temperature for 1 hour. The peptide solution was diluted 6-fold with water, and stirred at 4° C. for 3-5 days. The progress of peptide oxidation was monitored by HPLC. The endpoint of the oxidation process was the complete disappearance of free thiols, determined by Ellman reaction. (Method 2 was used in the preparation of SNX-236 and SNX-239).

DETD Rat brain synaptosomal membranes were incubated with a concentration of radiolabeled ligand approximating the K_{sub}.d of the ligand for its binding site, for a period of time sufficient to achieve equilibrium binding. A high concentration of unlabeled ligand was then added to the **mixture**, and the incubation continued. At time intervals, samples of the **mixture** were tested for binding of radiolabeled compound. As shown in FIG. 7, SNX-111 exhibited reversible binding with a dissociation half-time of about 2 min. Likewise, SNX-183 binding exhibited reversible binding with a dissociation half-time of about 5 min. In contrast, radiolabeled SNX-124 showed no dissociation from its binding site over the time period studied (60 min).

DETD Guinea pigs (300-400 gms) were decapitated and the ileum removed. A section of ileum about 6 cm from the caecum was placed immediately into Krebb's modified buffer maintained at 37° C. in a water bath, and aerated with a **mixture** of 95% O_{sub}.2 and 5% CO_{sub}.2. The buffer contains: KCl, 4.6 mM; KH_{sub}.2 PO_{sub}.4, 1.2 mM; MgSO_{sub}.4, 1.2 mM; Glucose, 10.0 mM; NaCl 118.2 mM; NaHCO_{sub}.3, 24.8 mM; CaCl_{sub}.2, 2.5 mM.

ACCESSION NUMBER: 1998:128233 USPATFULL
TITLE: Method of treating inflammation
INVENTOR(S): Justice, Alan, Sunnyvale, CA, United States
Singh, Tejinder, Palo Alto, CA, United States
Gohil, Kishor Chandra, Richmond, CA, United States
Valentino, Karen L., San Carlos, CA, United States
Miljanich, George P., Redwood City, CA, United States
PATENT ASSIGNEE(S): Neurex Corporation, Menlo Park, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5824645		19981020
APPLICATION INFO.:	US 1996-742774		19961101 (8)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1996-675354, filed on 3 Jul 1996 which is a continuation of Ser. No. US 1993-49794, filed on 15 Apr 1993, now patented, Pat. No. US 5587454 which is a continuation-in-part of Ser. No. US 1991-814759, filed on 30 Dec 1991, now abandoned		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Davenport, Avis M.		
LEGAL REPRESENTATIVE:	Stratford, Carol A., Dehlinger, Peter J.		

NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 51 Drawing Figure(s); 26 Drawing Page(s)
LINE COUNT: 2492
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L57 ANSWER 13 OF 13 USPATFULL on STN

L13 ANSWER 38 OF 48 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

AN 96317879 EMBASE

DN 1996317879

TI Two human paramyotonia congenita mutations have opposite effects on
lidocaine block of Na⁺ channels expressed in a mammalian cell line.

AU Fan Z.; George A.L. Jr.; Kyle J.W.; Makielski J.C.

CS Department of Medicine, University of Chicago, Chicago, IL, United States

SO Journal of Physiology, (1996) 496/1 (275-286).

ISSN: 0022-3751 CODEN: JPHYA7

CY United Kingdom

DT Journal; Article

FS 030 Pharmacology

037 Drug Literature Index

LA English

SL English

AB 1. Two mutant human skeletal muscle voltage-gated Na⁺ channel α -
subunits (hSkM1), with mutations found in patients with hereditary
paramyotonia congenita (T1313M on the III-IV linker and R1448C on the
outside of S4 of repeat IV), and wild-type hSkM1 channels were expressed
in a human embryonic kidney cell line (tsA201) using recombinant cDNA. 2.
Compared with wild-type, both mutants exhibited altered inactivation
phenotypes. Current decay was slowed for both, but voltage-dependent
availability from inactivation was shifted in the negative direction for
R1448C and in the positive direction for T1313M. 3. The hypothesis that a
local anaesthetic, lidocaine (lignocaine), binds primarily to the
inactivated state to block the channel was reassessed by testing lidocaine
block of these two mutants and the wild-type channel. 4. T1313M showed
reduced phasic block, but R1448C showed increased phasic block for trains
of depolarizations. 5. Rest block (from -120 mV) was increased for R1448C
(IC_{50.simeq} 0.2 mM) and decreased for T1313M (IC_{50.simeq} 1.3 mM)
compared with wild-type (IC_{50.simeq} 0.5 mM), but these differences were
diminished at a holding potential of -150 mV, suggesting that the
differences were caused by binding to the inactivated state rather than a
different affinity of lidocaine for the resting state. 6. Inactivated
state affinity measured from lidocaine-induced shifts in voltage-dependent
availability was reduced for T1313M (K(d) = 63 μ M) but little changed
for R1448C (K(d) = 14 μ M) compared with wild-type (K(d) = 11 μ M).
Two pulse recovery protocols showed faster recovery from lidocaine block
for T1313M and slower recovery for R1448C. Together these accounted for
the opposite effects on lidocaine phasic block observed for the mutant
channels. 7. Neither mutation is located at a putative lidocaine binding
site in domain 4 S6, yet both affected lidocaine block. The data
suggest that R1448C altered phasic lidocaine block mainly through altered
kinetics, but T1313M altered block through a change in affinity for the
inactivated state. These findings have implications for drug therapy of
paramyotonia congenita, and also provide an insight into structural
requirements for drug affinity.

CT Medical Descriptors:

*gene mutation

*sodium channel

animal cell

article

cell line

drug binding

embryo

human

kidney cell

priority journal

thomsen disease

Drug Descriptors:

*lidocaine: PD, pharmacology

*sodium ion: EC, endogenous compound

ER 44 OF 48 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.

on STN

AN 94313466 EMBASE

DN 1994313466

TI Molecular determinants of state-dependent block of Na⁺ channels by local anesthetics.

AU Ragsdale D.S.; McPhee J.C.; Scheuer T.; Catterall W.A.

CS Department of Pharmacology, University of Washington, Seattle, WA 98195, United States

SO Science, (1994) 265/5179 (1724-1728).

ISSN: 0036-8075 CODEN: SCIEAS

CY United States

DT Journal; Article

FS 002 Physiology

024 Anesthesiology

030 Pharmacology

037 Drug Literature Index

LA English

SL English

AB **Sodium** ion (Na⁺) **channels**, which initiate the action potential in electrically excitable cells, are the molecular targets of local anesthetic drugs. Site-directed mutations in transmembrane segment S6 of domain IV of the Na⁺ channel α **subunit** from rat brain selectively modified drug binding to resting or to open and inactivated channels when expressed in *Xenopus* oocytes. Mutation F1764A, near the middle of this segment, decreased the affinity of open and inactivated channels to 1 percent of the wild-type value, resulting in almost complete abolition of both the use-dependence and voltage-dependence of drug block, whereas mutation N1769A increased the affinity of the resting channel 15-fold. Mutation I1760A created an access pathway for drug molecules to reach the receptor site from the extracellular side. The results define the location of the local anesthetic receptor site in the pore of the Na⁺ channel and identify molecular determinants of the state-dependent binding of local anesthetics.

CT Medical Descriptors:

***sodium channel**

animal cell

animal tissue

article

brain

nonhuman

oocyte

priority journal

rat

site directed mutagenesis

toad

Drug Descriptors:

***local anesthetic agent: PD, pharmacology**

etidocaine

RN (etidocaine) 36637-18-0, 36637-19-1

L54 ANSWER 15 OF 15 USPATFULL on STN

DETD c. Neuropathic **Pain** Models. Analgesic potency of conopeptides can also be tested in animal models of neuropathic or neurogenic **pain**. One such model resembles the human condition termed causalgia or reflex sympathetic dystrophy (RSD) secondary to injury of a peripheral nerve. This condition is characterized by hyperesthesia (enhanced sensitivity to a natural stimulus), hyperalgesia (abnormal sensitivity to **pain**), allodynia (widespread tenderness, characterized by hypersensitivity to tactile stimuli), and spontaneous burning **pain**. In humans, neuropathic **pain** tends to be chronic and may be debilitating. This type of **pain** is generally considered to be non-responsive or only partially responsive to conventional **opioid** analgesic regimens (Jadad). In accordance with the invention, analgesic omega ~~conotoxin~~ peptides are effective in providing relief of neuropathic **pain**, as described below.

ACCESSION NUMBER: 96:118666 USPATFULL
TITLE: Omega conopeptide compositions
INVENTOR(S): Justice, Alan, Sunnyvale, CA, United States
Singh, Tejinder, Palo Alto, CA, United States
Gohil, Kishor C., Richmond, CA, United States
Valentino, Karen L., San Carlos, CA, United States
Miljanich, George P., Redwood City, CA, United States
PATENT ASSIGNEE(S): Neurex Corporation, Menlo Park, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5587454		19961224
APPLICATION INFO.:	US 1993-49794		19930415 (8)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1991-814759, filed on 30 Dec 1991, now abandoned		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Davenport, Avis M.		
LEGAL REPRESENTATIVE:	Stratford, Carol A., Dehlinger, Peter J.		
NUMBER OF CLAIMS:	3		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	51 Drawing Figure(s); 27 Drawing Page(s)		
LINE COUNT:	2510		
CAS INDEXING IS AVAILABLE FOR THIS PATENT.			

=>

L41 ANSWER 48 OF 78 USPATFULL on STN

DETD **Analgesic** potency of conopeptides can also be tested in animal models of neuropathic or neurogenic **pain**. One such model resembles the human condition termed causalgia or reflex sympathetic dystrophy (RSD) secondary to injury of a peripheral nerve. This condition is characterized by hyperesthesia (**enhanced** sensitivity to a natural stimulus), hyperalgesia (abnormal sensitivity to **pain**), allodynia (widespread tenderness, characterized by hypersensitivity to tactile stimuli), and spontaneous burning **pain**. In humans, neuropathic **pain** tends to be chronic and may be debilitating. This type of **pain** is generally considered to be non-responsive or only partially responsive to conventional **opioid analgesic** regimens (Jadad). In accordance with the invention, **analgesic/omega conotoxin** peptides are effective in providing relief of neuropathic **pain**, as described below.

PI

US 5859186

19990112

1 mice used were male. n=8 for each curve; error bars indicate S.E.M.
DRWD [0019] FIG. 5 shows that cotreatment of male and female mice with orally-administered cholera **toxin** B subunit (CTXB) blocks acute, low-dose, morphine-induced hyperalgesic effects, thereby unmasking potent **opioid** analgesia. Tail-flick tests were performed at 52° C., as in FIGS. 1 and 2. A: Administration of 0.1 µg/kg morphine (Mor) (s.c.) resulted in characteristic hyperalgesia (.circle-solid.), as in FIG. 1:.circle-solid.. In contrast, after oral pretreatment of another group of mice with CTXB (added a day earlier to the drinking-water bottles, at a concentration of 1 µg/ml), low-dose, morphine-induced hyperalgesia was blocked, and prominent **opioid** analgesia was unmasked (.smallcircle.). B: The protocol that was used in A also was carried out on a group of female mice, resulting in a similar demonstration of oral-CTXB blockade of morphine-induced hyperalgesia and a similar unmasking of **opioid** analgesia (.smallcircle.). C, D: After a second day of oral-CTXB treatment, the same groups of male and female mice were assayed by testing the effect of a 10,000-fold **increase** in acute morphine dose (1 mg/kg; s.c.). Much larger **increases** in the magnitude and duration of morphine's antinociceptive effects were noted in CTXB-treated mice (.smallcircle.). Although morphine's **analgesic** effects in the control group of female mice were considerably weaker, resulting in hyperalgesia by 2 h after **opioid** injection (.circle-solid.), the CTXB-treated group showed prominent morphine analgesia during the entire test period (.smallcircle.). n=8 for each curve; error bars indicate S.E.M.; *=oral pretreatment of CTXB (1 µg/ml) in drinking water on previous day

PI

US 2002137761 A1 20020926

L42 ANSWER 5 OF 97 CAPLUS COPYRIGHT 2004 ACS on STN

AN 2001:794730 CAPLUS

DN 136:16414

ED Entered STN: 01 Nov 2001

TI Cholera toxin-B subunit blocks excitatory opioid receptor-mediated hyperalgesic effects in mice, thereby unmasking potent opioid analgesia and attenuating opioid tolerance/dependence

AU Shen, Ke-Fei; Crain, Stanley M.

CS Department of Neuroscience, Albert Einstein College of Medicine, Yeshiva University, Bronx, NY, 10461, USA

SO Brain Research (2001), 919(1), 20-30

CODEN: BRREAP; ISSN: 0006-8993

PB Elsevier Science B.V.

DT Journal

LA English

CC 4-5 (Toxicology)

Section cross-reference(s): 1

AB In a previous study we demonstrated that injection (i.p.) of low doses of GM1 ganglioside in mice rapidly attenuates morphine's **analgesic** effects. This result is consonant with our electrophysiol. studies in nociceptive types of dorsal root ganglion (DRG) neurons in culture, which showed that exogenous GM1 rapidly **increased** the efficacy of excitatory (Gs-coupled) **opioid** receptor functions. By contrast, treatment of DRG neurons with the nontoxic B-subunit of cholera **toxin** (CTX-B) which binds selectively to GM1, blocked the excitatory, but not inhibitory, effects of morphine and other bimodally acting opioid agonists, thereby resulting in a net **increase** in inhibitory opioid potency. The present study provides more direct evidence that endogenous GM1 plays a physiol. role in regulating excitatory opioid receptor functions in vivo by demonstrating that cotreatment with remarkably low doses of CTX-B (10 ng/kg, s.c.) selectively blocks hyperalgesic effects elicited by morphine or by a kappa opioid agonist, thereby unmasking potent opioid analgesia. These results are comparable to the effects of cotreatment of mice with morphine plus an ultra-low dose of the opioid antagonist, naltrexone (NTX) which blocks opioid-induced hyperalgesic effects, unmasking potent opioid analgesia. Low-dose NTX selectively blocks excitatory opioid receptors at their recognition site, whereas CTX-B binds to, and interferes with, a putative allosteric GM1 regulatory site on excitatory opioid receptors. Furthermore, chronic cotreatment of mice with morphine plus CTX-B attenuates development of opioid tolerance and phys. dependence, as previously shown to occur during cotreatment with low-dose NTX.

ST cholera toxin B subunit excitatory opioid receptor hyperalgesia

IT G proteins (guanine nucleotide-binding proteins)

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(Gs (adenylate cyclase-stimulating); cholera toxin-B subunit blocks excitatory opioid receptor-mediated hyperalgesic effects in mice, thereby unmasking potent opioid analgesia and attenuating opioid tolerance/dependence)

IT Drug dependence

(cholera toxin-B subunit blocks excitatory opioid receptor-mediated hyperalgesic effects in mice, thereby unmasking potent opioid analgesia and attenuating opioid tolerance/dependence)

IT Opioid receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(cholera toxin-B subunit blocks excitatory opioid receptor-mediated hyperalgesic effects in mice, thereby unmasking potent opioid analgesia and attenuating opioid tolerance/dependence)

IT Toxins

RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)

(cholera, subunit B; cholera toxin-B subunit blocks excitatory opioid receptor-mediated hyperalgesic effects in mice, thereby unmasking potent opioid analgesia and attenuating opioid tolerance/dependence)

IT Pain
(hyperalgesia; cholera toxin-B subunit blocks excitatory opioid receptor-mediated hyperalgesic effects in mice, thereby unmasking potent opioid analgesia and attenuating opioid tolerance/dependence)

IT Nerve
(neuron, dorsal root ganglion; cholera toxin-B subunit blocks excitatory opioid receptor-mediated hyperalgesic effects in mice, thereby unmasking potent opioid analgesia and attenuating opioid tolerance/dependence)

IT Analgesia
(opioid; cholera toxin-B subunit blocks excitatory opioid receptor-mediated hyperalgesic effects in mice, thereby unmasking potent opioid analgesia and attenuating opioid tolerance/dependence)

IT Ganglion
(spinal, neurons; cholera toxin-B subunit blocks excitatory opioid receptor-mediated hyperalgesic effects in mice, thereby unmasking potent opioid analgesia and attenuating opioid tolerance/dependence)

IT Opioids
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(κ -; cholera toxin-B subunit blocks excitatory opioid receptor-mediated hyperalgesic effects in mice, thereby unmasking potent opioid analgesia and attenuating opioid tolerance/dependence)

IT Opioids
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(μ -; cholera toxin-B subunit blocks excitatory opioid receptor-mediated hyperalgesic effects in mice, thereby unmasking potent opioid analgesia and attenuating opioid tolerance/dependence)

IT 57-27-2, Morphine, biological studies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(cholera toxin-B subunit blocks excitatory opioid receptor-mediated hyperalgesic effects in mice, thereby unmasking potent opioid analgesia and attenuating opioid tolerance/dependence)

IT 37758-47-7, Ganglioside GM1
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cholera toxin-B subunit blocks excitatory opioid receptor-mediated hyperalgesic effects in mice, thereby unmasking potent opioid analgesia and attenuating opioid tolerance/dependence)

RE.CNT 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

- (1) Abul-Husn, N; Soc Neurosci Abstr 2000, V26, P1665
- (2) Agnati, L; Acta Physiol Scand 1983, V117, P311 CAPLUS
- (3) Apfel, S; Neuroscience 1995, V68, P1199 CAPLUS
- (4) Arts, K; Pharmacol Biochem Behavior 1993, V46, P623 CAPLUS
- (5) Berry-Kravis, E; J Neurochem 1985, V45, P1739 CAPLUS
- (6) Bohn, L; Nature 2000, V408, P720 CAPLUS
- (7) Casey, P; J Biol Chem 1988, V263, P2577 CAPLUS
- (8) Cassel, D; Proc Natl Acad Sci USA 1977, V74, P3307 CAPLUS
- (9) Chalazonitis, A; Neuroscience 1986, V17, P1181 CAPLUS
- (10) Chen, G; Brain Res 1988, V462, P372 CAPLUS
- (11) Crain, S; Ann N Y Acad Sci 1998, V8

L13 ANSWER 5 OF 48 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

AN 2003089968 EMBASE

TI Differential interactions of lamotrigine and related drugs with
transmembrane segment IVS6 of voltage-gated **sodium**
channels.

AU Liu G.; Yarov-Yarovoy V.; Nobbs M.; Clare J.J.; Scheuer T.; Catterall W.A.

CS W.A. Catterall, Department of Pharmacology, Mailstop 357280, University of
Washington, Seattle, WA 98195-7280, United States. wcatt@u.washington.edu

SO Neuropharmacology, (2003) 44/3 (413-422).
Refs: 35
ISSN: 0028-3908 CODEN: NEPHBW

CY United Kingdom

DT Journal; Article

FS 008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index

LA English

SL English

AB Voltage-gated **sodium channels** are blocked by local
anesthetic and anticonvulsant drugs. A receptor site for local anesthetics
has been defined in transmembrane segment **S6** in domain IV (IVS6)
of the α **subunit**, but the anticonvulsant lamotrigine and
related compounds have more complex structures than local anesthetics and
may interact with additional amino acid residues. Apparent K(D) values for
inactivated-state block of rat brain type IIA **sodium**
channels expressed in *Xenopus* oocytes were 31.9 μ M, 17.3 μ M,
3.7 μ M and 10.3 μ M for lamotrigine and compounds 227c89, 4030w92 and
619c89, respectively. Compound 619c89 was the strongest
frequency-dependent blocker, which correlated with higher affinity and a
five-fold slower recovery from drug block compared to lamotrigine.
Examination of lamotrigine block of mutant **sodium**
channel α **subunits**, in which alanine had been
substituted for each individual amino acid in IVS6, identified mutations
I1760A, F1764A and Y1771A as causing the largest reductions in affinity
(six-, seven- and 12-fold, respectively). The ratios of effects of these
three mutations differed for compounds 227c89, 4030w92, and 619c89. The
amino acid residues interacting with these pore-blocking drugs define a
surface of IVS6 that is exposed to the pore and may rotate during gating.
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CT Medical Descriptors:
***sodium channel**
*channel gating
protein expression
Xenopus
oocyte
drug effect
drug mechanism
amino acid substitution
protein structure
protein binding
binding affinity
drug protein binding
protein domain
drug binding
nonhuman
rat
controlled study
animal tissue
animal cell
article
priority journal

Drug Descriptors:

*lamotrigine: PD, pharmacology
*anticonvulsive agent: PD, pharmacology
*analgesic agent: PD, pharmacology
*sipatrigine: PD, pharmacology
*membrane protein
alanine
mutant protein
neuroprotective agent: PD, pharmacology

protein subunit

2,4 diamino 5 (2,3 dichlorophenyl) 6 fluoromethylpyrimidine
227c89

RN (lamotrigine) 84057-84-1; (sipatrigine) 130800-90-7; (alanine) 56-41-7,
6898-94-8

CN (1) 4030w92; 227c89; 619c89

CO (1) Glaxo SmithKline

L13 ANSWER 13 OF 48 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

AN 2001159308 EMBASE

TI Disparate role of Na(+) channel D2-S6 residues in batrachotoxin
and local anesthetic action.

AU Wang S.-Y.; Barile M.; Ging Kou Wang

CS Dr. G.K. Wang, Department of Anesthesia, Harvard Medical School, Brigham
and Women's Hospital, 75 Francis St., Boston, MA 02115, United States.
wang@zeus.bwh.harvard.edu

SO Molecular Pharmacology, (2001) 59/5 (1100-1107).
Refs: 34
ISSN: 0026-895X CODEN: MOPMA3

CY United States

DT Journal; Article

FS 024 Anesthesiology
030 Pharmacology
037 Drug Literature Index

LA English

SL English

AB Batrachotoxin (BTX) stabilizes the voltage-gated Na(+) channels in their
open conformation, whereas local anesthetics (LAs) block Na(+) conductance. Site-directed mutagenesis has identified clusters of common residues at D1-S6, D3-S6, and D4-S6 segments within the α -subunit Na(+) channel that are critical for binding of these two types of ligands. In this report, we address whether segment ~~D2-S6~~ is similarly involved in both BTX and LA actions. Thirteen amino acid positions from G783 to L795 of the rat skeletal muscle Na(+) channel (μ 1/Skml) were individually substituted with a lysine residue. Four mutants (N784K, L785K, V787K, and L788K) expressed sufficient Na(+) currents for further studies. Activation and/or inactivation gating was altered in mutant channels; in particular, μ 1-V787K displays enhanced slow inactivation and exhibited use-dependent inhibition of peak Na(+) currents during repetitive pulses. Two of these four mutants, μ 1-N784K and μ 1-L788K, were completely resistant to 5 μ M BTX. This BTX-resistant phenotype could be caused by structural perturbations induced by a lysine point mutation in the D2-S6 segment. However, these two BTX-resistant mutants remained quite sensitive to bupivacaine block with affinity for inactivated Na(+) channels (K(1)) of \approx 10 μ M or less, which suggests that μ 1-N784 and μ 1-L788 residues are not in close proximity to the LA binding site.

CT Medical Descriptors:
*sodium channel
electric potential
sodium conductance
site directed mutagenesis
ligand binding
amino acid analysis
sodium current
phenotype
point mutation
binding site
drug mechanism
human
nonhuman
rat
controlled study
human cell
animal tissue
article
priority journal
Drug Descriptors:
*batrachotoxin: PD, pharmacology
*local anesthetic agent: PD, pharmacology

lysine
RN (batrachotoxin) 23509-16-2; (lysine) 56-87-1, 6899-06-5, 70-54-2

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(neuro-, $\beta 1$ **sodium channel subunit** modifies interactions of neurotoxins and local anesthetics with rat brain IIA α **sodium channel** in isolated membranes but not in intact cells)

IT Ion channel

Ion channel blockers

(sodium, $\beta 1$ **sodium channel subunit** modifies interactions of neurotoxins and local anesthetics with rat brain IIA α **sodium channel** in isolated membranes but not in intact cells)

IT 50-47-5, Desipramine 50-48-6, Amitriptyline 71-62-5, Veratridine
94-24-6, Tetracaine 137-58-6, Lidocaine 390-64-7, Prenylamine
31828-71-4, Mexiletine 31883-05-3, Moricizine 52468-60-7, Flunarizine
98225-48-0, Brevetoxin 98444-62-3, RU 39568 149838-21-1, PD85639

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

($\beta 1$ **sodium channel subunit** modifies interactions of neurotoxins and local anesthetics with rat brain IIA α **sodium channel** in isolated membranes but not in intact cells)

IT 7440-23-5, Sodium, biological studies

RL: BSU (Biological study, unclassified); BIOL (Biological study)

($\beta 1$ **sodium channel subunit** modifies interactions of neurotoxins and local anesthetics with rat brain IIA α **sodium channel** in isolated membranes but not in intact cells)

L24 ANSWER 1 OF 9 USPATFULL on STN

SUMM The present invention includes methods of producing potent long-lasting local anesthesia and analgesia, comprising administering a pharmaceutically acceptable composition of a long-acting **sodium channel blocking** compound, wherein the compound binds to the extracellular mouth of the **sodium channel**. In this manner **sodium channel** activity is **inhibited** by a mechanism distinct from that of local anesthetics, such as procaine, lidocaine and tetracaine. Preferably, such methods achieve potent local analgesia and anesthesia of long duration up to 6 hours. Preferred compounds include toxins or analogs thereof that specifically bind to a site formed in part by an extracellular region of the alpha **subunit** of a **sodium channel**. Most preferred compounds comprise the class of toxins and analogs that specifically bind to a site formed by the **SS1** and **SS2** extracellular regions of the alpha **subunit** of a **sodium channel**, wherein such compounds include tetrodotoxin, saxitoxin and analogs thereof. Surprisingly, these long-acting **sodium channel blocking** compounds, which are well known potent neurotoxins, provide potent long-lasting local analgesia and anesthesia without evident side-effects.

SUMM The present invention also includes a composition comprising a conventional local anesthetic compound that is a **sodium channel blocking** compound and a compound that binds to the **SS1** or **SS2 subunit** of a **sodium channel**. The composition of the invention provides a synergistic effect of its component compounds to provide either or both of a more potent or a longer anesthetic effect.

DETD Synergistic compositions of the invention comprise at least one compound that specifically binds to the **SS1** or to the **SS2 subunit** of a **sodium channel**, together with at least one conventional local anesthetic. In such synergistic compositions, the compound that binds to the **SS1** or **SS2 subunit** of a **sodium channel** is preferably saxitoxin or tetrodotoxin, more preferably tetrodotoxin. The conventional local anesthetic is a **sodium channel blocking** compound, preferably tetracaine. In the compositions of the invention, the compound that binds to the **SS1** or **SS2 subunit** of a **sodium channel** is typically present in an amount of from 1 to 10 mM, more typically in an amount of from 1 to 3 mM. The conventional local anesthetic is typically present in an amount representing one-half to two times its effective concentration, usually in an amount of from 0.2 to 5 percent by weight of the composition. Depending upon the components chosen as the **SS1** or **SS2** binding ingredient and as the local anesthetic, the composition can be prepared by mixing the ingredients immediately before administration, or can be mixed and then stored for later administration. This choice will depend in part upon what pH provides good stability to each ingredient. Ingredients requiring widely disparate pH for long-term stability should be mixed just prior to administration.

CLM What is claimed is:

1. A method of producing local analgesia or anesthesia in nerve tissue of a mammal experiencing pain, comprising: administering to dental pulp or a trigeminal nerve region of the mammal a first injection of a composition comprising a local anesthetic; and administering a second injection of a composition comprising a compound that binds to an **SS1** or **SS2 subunit** of a **sodium channel**.

4. The method of claim 1, wherein the compound that binds to the **SS1** or

SS2 subunit of the **sodium channel** is tetrodotoxin.

7. The method of claim 1, wherein the compound that binds to the SS1 or SS2 subunit of the **sodium channel** is saxitoxin.

PI US 6599906 B1 20030729

L66 ANSWER 5 OF 118 CAPLUS COPYRIGHT 2004 ACS on STN
 AN 1993:443457 CAPLUS
 DN 119:43457
 ED Entered STN: 07 Aug 1993
 TI Site-directed mutagenesis of the putative pore region of the rat IIA
sodium channel
 AU Kontis, Kris J.; Goldin, Alan L.
 CS Dep. Microbiol. Mol. Genet., Univ. California, Irvine, CA, 92717, USA
 SO Molecular Pharmacology (1993), 43(4), 635-44
 CODEN: MOPMA3; ISSN: 0026-895X
 DT Journal
 LA English
 CC 6-1 (General Biochemistry)
 AB Site-directed mutagenesis was used to examine the functional role of each
 of the eight acidic amino acid residues in the region between proposed
 transmembrane segments 5 and 6 (S5-S6) of domain II of the rat brain IIA
sodium channel α subunit. The mutant
sodium channels were expressed in *Xenopus* oocytes and
 analyzed by two-microelectrode voltage clamping with respect to
 voltage-dependent activation, inactivation, ion selectivity, and
 sensitivity to the pore-blocking neurotoxins tetrodotoxin (TTX) and
 saxitoxin (STX). None of the mutations had significant effects on
 voltage-dependent gating, ion selectivity, or block by protons or calcium.
 Three of the mutations had significant effects on the sensitivity of the
 channel to block by TTX and STX. Neutralization of neg. charges at
 positions 942 and 945 greatly reduced the block by TTX and STX, suggesting
 that these two residues interact directly with the toxins. Substitution
 of a nearby neg. charge at position 949 resulted in a smaller decrease in
 TTX and STX block, although anal. of TTX block of this mutant at low ionic
 strength suggests that the interaction is not simply by an electrostatic
 through-space mechanism. None of the other five mutations had any effects
 on block by either TTX or STX. The two acidic residues that had dramatic
 effects on toxin binding had significantly smaller effects at a
 depolarized membrane potential. The **sodium channel**
 interacts with TTX and STX with higher affinity at depolarized potentials,
 so these two residues must make a greater contribution to toxin binding in
 the low affinity state. These results define a small segment of the
sodium channel α subunit domain II S5-S6
 region that interacts with TTX and STX and therefore must lie near the
 mouth of the channel pore.
 ST **sodium channel** IIA pore tetrodotoxin saxitoxin;
 transport **sodium channel** IIA tetrodotoxin saxitoxin
 IT Brain, composition
 (sodium channel IIA of, α -subunit
 domain II S5-S6 region of, pore region location and tetrodotoxin and
 saxitoxin interaction of)
 IT Biological transport
 (channel-mediated, of sodium, by brain **sodium channel**
 IIA, tetrodotoxin and saxitoxin inhibition of, channel pore region
 structure determination for)
 IT Electric activity
 (charge, of **sodium channel** IIA residues 942 and
 945, tetrodotoxin and saxitoxin interaction in relation to)
 IT Cations
 (monovalent, **sodium channel** IIA wild-type and
 mutant form selectivity for)
 IT Electric activity
 (potential, membrane, tetrodotoxin and saxitoxin interaction with
sodium channel IIA pore region acidic residues
 response to)
 IT Ion channel
 (sodium, IIA, α -subunit domain II S5-S6-region of, of
 brain, pore region location and tetrodotoxin and saxitoxin interaction

of)

IT 56-86-0, Glutamic acid, biological studies
 RL: BIOL (Biological study)
 (in **sodium channel** IIA α - **subunit**
 positions 942 and 945, tetrodotoxin and saxitoxin binding and block
 dependence on, membrane potential in relation to)

IT 56-84-8, Aspartic acid, biological studies
 RL: BIOL (Biological study)
 (in **sodium channel** IIA α - **subunit**
 position 949, saxitoxin and tetrodotoxin block in relation to)

IT 4368-28-9, Tetrodotoxin 35523-89-8, Saxitoxin
 RL: BIOL (Biological study)
 (**sodium channel** IIA inhibition by and binding of,
 pore region acidic residues in)

IT 7439-93-2, Lithium, biological studies 25215-10-5, **Guanidinium**
 RL: BIOL (Biological study)
 (**sodium channel** IIA wild-type and mutant form
 selectivity for)

IT 7440-70-2, Calcium, biological studies 12408-02-5, Hydrogen ion,
 biological studies
 RL: BIOL (Biological study)
 (**sodium channel** IIA wild-type and mutant forms
 blocking by)

IT 7440-23-5, Sodium, biological studies
 RL: PRP (Properties)
 (transfer of, by brain **sodium channel** IIA,
 tetrodotoxin and saxitoxin inhibition of, channel pore region structure
 determinant for)

L12 ANSWER 23 OF 55 CAPLUS COPYRIGHT 2004 ACS on STN
 AN 1994:621058 CAPLUS
 DN 121:221058
 ED Entered STN: 12 Nov 1994
 TI Molecular determinants of state-dependent **block** of Na⁺ channels
 by local anesthetics
 AU Ragsdale, David S.; McPhee, Jancy C.; Scheuer, Todd; Catterall, William A.
 CS Department Pharmacology, University Washington, Seattle, WA, 98195, USA
 SO Science (Washington, DC, United States) (1994), 265(5179), 1724-8
 CODEN: SCIEAS; ISSN: 0036-8075
 DT Journal
 LA English
 CC 1-3 (Pharmacology)
 AB **Sodium** ion (Na⁺) **channels**, which initiate the action
 potential in elec. excitable cells, are the mol. targets of local
 anesthetic drugs. Site-directed mutations in transmembrane segment
S6 of domain IV of the Na⁺ channel α **subunit** from
 rat brain selectively modified drug binding to resting or to open and
 inactivated channels when expressed in Xenopus oocytes. Mutation F1764A,
 near the middle of this segment, decreased the affinity of open and
 inactivated channels to 1 percent of the wild-type value, resulting in
 almost complete abolition of both the use-dependence and
 voltage-dependence of drug **block**, whereas mutation N1769A
 increased the affinity of the resting channel 15-fold. Mutation I1760A
 created an access pathway for drug mols. to reach the receptor site from
 the extracellular side. The results define the location of the local
 anesthetic receptor site in the pore of the Na⁺ channel and identify mol.
 determinants of the state-dependent binding of local anesthetics.
 ST mol determinant **sodium channel** local anesthetic
 IT Molecular structure-biological activity relationship
 (in mol. determinants of state-dependent **block** of
sodium channels by local anesthetics)
 IT Anesthetics
 (local, mol. determinants of state-dependent **block** of
sodium channels by local anesthetics)
 IT Ion **channel blockers**
 (**sodium**, mol. determinants of state-dependent **block**
 of **sodium channels** by local anesthetics)
 IT 36637-18-0, Etidocaine
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological
 study, unclassified); PRP (Properties); BIOL (Biological study)
 (mol. determinants of state-dependent **block** of **sodium**
channels by local anesthetics)

L12 ANSWER 20 OF 55 CAPLUS COPYRIGHT 2004 ACS on STN
 AN 1996:621632 CAPLUS
 DN 125:292812
 ED Entered STN: 19 Oct 1996
 TI Two human paramyotonia congenita mutations have opposite effects on
 lidocaine **block** of Na⁺ channels expressed in a mammalian cell
 line
 AU Fan, Zheng; George, Alfred L., Jr.; Kyle, John W.; Makielski, Jonathan C.
 CS Dep. Med., Univ. Wisconsin, Madison, WI, USA
 SO Journal of Physiology (Cambridge, United Kingdom) (1996), 496(1), 275-286
 CODEN: JPHYA7; ISSN: 0022-3751
 PB Cambridge University Press
 DT Journal
 LA English
 CC 1-11 (Pharmacology)
 Section cross-reference(s): 3, 14
 AB Two mutant human skeletal muscle voltage-gated Na⁺ channel α -
subunits (hSkM1), with mutations found in patients with hereditary
 paramyotonia congenita (T1313M on the III-IV linker and R1448C on the
 outside of S4 of repeat IV), and wild-type hSkM1 channels were expressed
 in a human embryonic kidney cell line (tsA201) using recombinant cDNA.
 Compared with wild-type, both mutants exhibited altered inactivation
 phenotypes. Current decay was slowed for both, but voltage-dependent
 availability from inactivation was shifted in the neg. direction for
 R1448C and in the pos. direction for T1313M. The hypothesis that a local
 anesthetic, lidocaine (lignocaine), binds primarily to the inactivated
 state to **block** the channel was reassessed by testing lidocaine
block of these two mutants and the wild-type channel. T1313M
 showed reduced phasic **block**, but R1448C showed increased phasic
block for trains of depolarizations. Rest **block** (from
 -120 mV) was increased for R1448C (IC₅₀ \approx 0.2 mM) and decreased
 for T1313M (IC₅₀ \approx 1.3 mM) compared with wild-type (IC₅₀ \approx
 0.5 mM), but these differences were diminished at a holding potential of
 -150 mV, suggesting that the differences were caused by binding to the
 inactivated state rather than a different affinity of lidocaine for the
 resting state. Inactivated state affinity measured from lidocaine-induced
 shifts in voltage-dependent availability was reduced for T1313M (K_d = 63
 μ M) but little changed for R1448C (K_d = 14 μ M) compared with
 wild-type (K_d = 11 μ M). Two pulse recovery protocols showed faster
 recovery from lidocaine **block** for T1313M and slower recovery for
 R1448C. Together these accounted for the opposite effects on lidocaine
 phasic **block** observed for the mutant channels. Neither mutation is
 located at a putative lidocaine binding site in domain 4 S6, yet
 both affected lidocaine **block**. The data suggest that R1448C
 altered phasic lidocaine **block** mainly through altered kinetics,
 but T1313M altered **block** through a change in affinity for the
 inactivated state. These findings have implications for drug therapy of
 paramyotonia congenita, and also provide an insight into structural
 requirements for drug affinity.
 ST paramyotonia congenita mutation lidocaine **sodium channel**
 IT Mutation
 (human paramyotonia congenita mutations have opposite effects on
 lidocaine **block** of Na⁺ channels expressed in a mammalian cell
 line)
 IT Anesthetics
 (local, human paramyotonia congenita mutations have opposite effects on
 lidocaine **block** of Na⁺ channels expressed in a mammalian cell
 line)
 IT Muscle, disease
 (paramyotonia congenita, human paramyotonia congenita mutations have
 opposite effects on lidocaine **block** of Na⁺ channels expressed
 in a mammalian cell line)
 IT Ion **channel**

(**sodium**, human paramyotonia congenita mutations have opposite effects on lidocaine **block** of Na⁺ channels expressed in a mammalian cell line)

IT 137-58-6, Lidocaine

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(human paramyotonia congenita mutations have opposite effects on lidocaine **block** of Na⁺ channels expressed in a mammalian cell line)

L12 ANSWER 16 OF 55 CAPLUS COPYRIGHT 2004 ACS on STN

AN 1998:518608 CAPLUS

DN 129:325960

ED Entered STN: 20 Aug 1998

TI Effects of temperature and mexiletine on the F1473S Na⁺ channel mutation causing paramyotonia congenita

AU Fleischhauer, Richard; Mitrovic, Nenad; Deymeer, Feza; Lehmann-Horn, Frank; Lerche, H.

CS Department of Applied Physiology, University of Ulm, Ulm, D-89069, Germany
SO Pfluegers Archiv (1998), 436(5), 757-765

CODEN: PFLABK; ISSN: 0031-6768

PB Springer-Verlag

DT Journal

LA English

CC 1-11 (Pharmacology)

Section cross-reference(s): 14

AB The F1473S mutation of the adult human skeletal muscle Na⁺ channel causes paramyotonia congenita, a disease characterized by muscle stiffness sometimes followed by weakness in a cold environment. The symptoms are relieved by the local anesthetic mexiletine. This mutation, which resides in the cytoplasmic S4-S5 loop in domain IV of the α -**subunit**, was studied by heterologous expression in HEK293 cells using standard patch-clamp techniques. Compared to wild-type (WT) channels, those with the F1473S mutation exhibit a twofold slowing of fast inactivation, an increased persistent Na⁺ current, a +18-mV shift in steady-state inactivation and a fivefold acceleration of recovery from fast inactivation; slow inactivation was similar for both clones. Single-channel recordings for the F1473S mutation revealed a prolonged mean open time and an increased number of channel reopenings that increased further upon cooling. The pharmacol. effects of mexiletine on cells expressing either WT, F1473S or G1306E channels were studied. G1306E is a myotonia-causing mutation located within the inactivation gate that displays similar but stronger inactivation defects than F1473S. The hyperpolarizing shift in steady-state inactivation induced by mexiletine was almost identical for all three clones. In contrast, this agent had a reduced effectiveness on the phasic (use-dependent) **block** of Na⁺ currents recorded from the mutants: the relative order of **block** was WT>F1473S>G1306E. We suggest that the relative effectiveness of mexiletine is associated with the degree of abnormal channel inactivation and that the relative binding affinity of mexiletine is not substantially different between the mutations or the WT.

ST paramyotonia congenita **sodium channel** mutation
mexiletine

IT Mutation

Temperature effects, biological

(effects of temperature and mexiletine on the F1473S Na⁺ channel mutation causing paramyotonia congenita)

IT **Sodium channel**

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(effects of temperature and mexiletine on the F1473S Na⁺ channel mutation causing paramyotonia congenita)

IT Anesthetics

(local; effects of temperature and mexiletine on the F1473S Na⁺ channel mutation causing paramyotonia congenita)

IT Muscle, disease

(paramyotonia congenita; effects of temperature and mexiletine on the F1473S Na⁺ channel mutation causing paramyotonia congenita)

IT 31828-71-4, Mexiletine

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(effects of temperature and mexiletine on the F1473S Na⁺ channel mutation causing paramyotonia congenita)

RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE

- (1) An, R; Circ Res 1996, V79, P103 CAPLUS
- (2) Bean, B; J Gen Physiol 1983, V81, P613 CAPLUS
- (3) Bennett, P; Circ Res 1995, V77, P584 CAPLUS
- (4) Cannon, S; Neuron 1991, V6, P619 MEDLINE
- (5) Cannon, S; Neuron 1993, V10, P317 CAPLUS
- (6) Catterall, W; Annu Rev Biochem 1995, V64, P493 CAPLUS
- (7) Chahine, M; Neuron 1994, V12, P281 CAPLUS
- (8) Cummins, T; Biophys J 1996, V71, P227 CAPLUS
- (9) Fan, Z; J Physiol (Lond) 1996, V496, P275 CAPLUS
- (10) Filatov, G; J Gen Physiol 1998, V111, P703 CAPLUS
- (11) Hayward, L; Biophys J 1997, V72, P1204 CAPLUS
- (12) Hille, B; Ionic channels of excitable membranes, 2nd edn 1992, P390
- (13) Horn, R; Biophys J 1991, V60, P433
- (14) Lehmann-Horn, F; Muscle Nerve 1987, V10, P363 MEDLINE
- (15) Lehmann-Horn, F; Muscle Nerve 1987, V10, P633 MEDLINE
- (16) Lehmann-Horn, F; Myology, 2nd edn 1994, P1303
- (17) Lehmann-Horn, F; News Physiol Sci 1997, V12, P105 CAPLUS
- (18) Lehmann-Horn, F; Pflugers Arch 1991, V418, P3297
- (19) Lerche, H; Ann Neurol 1996, V39, P599 MEDLINE
- (20) Lerche, H; J Physiol (Lond) 1993, V470, P13 CAPLUS
- (21) Lerche, H; J Physiol (Lond) 1997, V505, P345 CAPLUS
- (22) McPhee, J; J Biol Chem 1995, V270, P12025 CAPLUS
- (23) McPhee, J; J Biol Chem 1998, V273, P1121 CAPLUS
- (24) Mitrovic, N; J Physiol (Lond) 1994, V478, P395 CAPLUS
- (25) Mitrovic, N; J Physiol (Lond) 1995, V487, P107 CAPLUS
- (26) Mitrovic, N; Neurosci Lett 1996, V213, P1
- (27) Ono, M; Cardiovasc Res 1994, V28, P973 CAPLUS
- (28) Patlak, J; J Gen Physiol 1982, V79, P333 CAPLUS
- (29) Patlak, J; J Gen Physiol 1986, V87, P305 CAPLUS
- (30) Qu, Y; Proc Natl Acad Sci USA 1995, V92, P11839 CAPLUS
- (31) Ragsdale, S; Science 1994, V265, P1724
- (32) West, J; Proc Natl Acad Sci USA 1992, V89, P10910 CAPLUS
- (33) Yang, N; Neuron 1996, V16, P113 CAPLUS
- (34) Yang, N; Proc Natl Acad Sci USA 1994, V91, P12785 CAPLUS

L24 ANSWER 8 OF 9 USPATFULL on STN

SUMM The present invention includes methods of producing long-lasting local anesthesia, comprising administering a pharmaceutically acceptable composition of a long-acting **sodium channel blocking** compound, wherein said compound binds to the extracellular mouth of the **sodium channel**, occluding the channel by a mechanism separate from that of local anesthetics, such as proparacaine. Preferably, such methods achieve local anesthesia of long duration, lasting at least 3 hours (3 to 10 hours), preferably at least 4 hours (4-10 hours), and most preferably at least 6 to 10 hours. Preferred compounds include toxins or analogs thereof that specifically bind to a site formed in part by an extracellular region of the alpha **subunit** of a **sodium channel**. Most preferred compounds comprise the class of toxins and analogs that specifically bind to a site formed by the **SS1** and **SS2** extracellular regions of the alpha **subunit** of a **sodium channel**, wherein such compounds include tetrodotoxin, saxitoxin and analogs thereof. Surprisingly, these long-acting **sodium channel blocking** compounds, which are well known, potent neurotoxins, provide long-lasting local anesthesia without **inhibiting** reepithelialization.

DETD "Long-acting **sodium channel blocking** compound" refers to a compound, e.g. a toxin or analog that, when administered to a mammal in an effective concentration, causes local anesthesia lasting at least 3 to 10 hours, and specifically binds to the extracellular mouth of the **sodium channel**, occluding the channel by a mechanism separate from that of local anesthetics, such as lidocaine, proparacaine. See J. F. Butterworth and G. R. Strichartz, *Anesthes.* 72:711-734 (1990). Long-acting **sodium channel blocking** compounds, when administered in a single dose, may effect local anesthesia of long duration, lasting at least 3 hours (3 to 10 hours), preferably at least 4 hours (4-10 hours), and most preferably at least 6 to 10 hours. Such long-acting **sodium channel blocking** compounds include compounds that specifically bind to a site formed in part by an extracellular region of the alpha **subunit** of a **sodium channel**. See Goodman & Gilman's, *The Pharmacological Basis of Therapeutics*, Ninth Edition 340-341 (1996); H. Terlau, et al., *Fed. Europ. Biochem. Soc.* 293(1-2): 93-96 (1991); *Encyclopedia of Molecular Biology*, pages 1127-1131 (ed. J. Kendrew 1994). Examples of long-acting **sodium channel blocking** compounds that bind to an extracellular site formed by the **SS1** and **SS2** segments of the alpha **subunit** include but are not limited to tetrodotoxin, saxitoxin, chiriquitoxin, GTTX (from *G. tamarensis*), gonyautoxins (GTX-I-V, GTX-I, GTX-II, GTX-III), neosaxitoxin, and derivatives and analogs thereof. D. J. Bower, et al., *Clinical Toxicology*, 18(7):813-863 (1981). Examples of long-acting **sodium channel blocking** compounds that bind to an extracellular site formed by the **SS3** and **SS4** segments of the alpha **subunit**, include but are not limited to alpha-scorpion toxin and sea anemone toxin. See Rogers, J. C. et al., *J. Biol. Chem.* 271(27):15950-15962 (1996).

CLM What is claimed is:

1. A method of producing local anesthesia in a partially or completely de-epithelialized tissue region of a mammal, comprising topically administering an anesthetically effective dose of a pharmaceutical composition consisting essentially of a long-acting **sodium channel blocking** compound, in a pharmaceutically suitable vehicle, to said de-epithelialized tissue region of said mammal, wherein said de-epithelialized tissue region is a corneal region, a region in the upper or lower gastrointestinal tract, or a genital lesion in the genital area.

2. The method of claim 1, wherein said long-acting **sodium channel** blocking compound does not inhibit re-epithelialization of said epithelial tissue region.
3. The method of claim 2, wherein said **sodium channel** blocking compound is administered every 6-8 hours for between about 24-72 hours.
4. The method of claim 2, wherein said long-acting **sodium channel** blocking compound is a compound capable of specifically binding to a site on an extracellular region of a **sodium channel** alpha subunit.
5. The method of claim 4, wherein said site is on an SS2 extracellular region of a **sodium channel** alpha subunit.
6. The method of claim 5, wherein said long-acting **sodium channel** blocking compound is tetrodotoxin.
10. The method of claim 5, wherein said long-acting **sodium channel** blocking compound is saxitoxin.
12. The method of claim 1, wherein said administering comprises instilling drops of said **sodium channel** blocking compound to the eye following corneal surgery.
15. A method of producing local anesthesia in an eye of a mammal, comprising topically administering to the corneal surface of the eye of said mammal, in an ophthalmically suitable vehicle, an anesthetically effective dose of a pharmaceutical composition consisting essentially of a long-acting **sodium channel** blocking compound, said corneal surface having an epithelial layer that is partially or completely de-epithelialized.
16. The method of claim 15, wherein said long-acting **sodium channel** blocking compound is a compound capable of specifically binding to a site on an extracellular region of a **sodium channel** alpha subunit, wherein said site is on either an SS1 region or an SS2 region.
17. The method of claim 16, wherein said long-acting **sodium channel** blocking compound is tetrodotoxin and said effective dose is administered from a formulation containing tetrodotoxin at a concentration between about 0.001-10 mM.
18. The method of claim 17, wherein said long-acting **sodium channel** blocking compound is tetrodotoxin and said effective dose is administered from a formulation containing tetrodotoxin at a concentration between about 0.01 mM to 0.2 mM.
20. A method of reducing pain in a mammal following corneal refractive surgery, comprising, topically administering to a partially or completely de-epithelialized corneal surface of an eye of said mammal, in an ophthalmically suitable vehicle, a pain reducing effective dose of a pharmaceutical composition consisting essentially of a long-acting **sodium channel** blocking compound.
23. A method of reducing pain in a mammal following corneal refractive surgery, comprising topically administering to a corneal surface of an eye of said mammal, in an ophthalmically suitable vehicle, a pain reducing effective dose of a pharmaceutical composition consisting essentially of a long-acting **sodium channel** blocking compound, wherein said administering is by applying to the eye of said

mammal a bandage contact lens, wherein said lens is capable of delivering said long-acting **sodium channel** blocking compound to said corneal surface.

31. A method of producing a non-toxic local anesthesia in an epithelial tissue region of a mammal, comprising topically administering an anesthetically effective dose of a pharmaceutical composition consisting essentially of a long-acting **sodium channel** blocking compound, in a pharmaceutically suitable vehicle comprising a citrate buffer at pH 4-8, to said epithelial tissue region of said mammal.

34. The method of claim 31, wherein said long-acting **sodium channel** blocking compound does not inhibit re-epithelialization of said epithelial tissue.

PI

US 6030974

20000229

L24 ANSWER 3 OF 9 USPATFULL on STN

- SUMM [0005] On the other hand, **sodium channel blocking** compounds that bind to the **SS1** or **SS2 subunit** of a **sodium channel**, particularly tetrodotoxin and saxitoxin, are found to possess a potent analgesic property (U.S. patent application Ser. No. 09/695,053). Tetrodotoxin is effective on all severe chronic pains. Tetrodotoxin is capable of providing analgesia in a mammal experiencing acute or chronic pain.
- SUMM [0008] The present invention is related to producing analgesia in mammals, in particular in humans, by co-administering synergistically effective amounts of (1) a **sodium channel blocking** compound that specifically binds to the **SS1** or **SS2 subunit** of a **sodium channel**, such as tetrodotoxin or saxitoxin or analogs thereof; and (2) an opioid analgesic agent. The present invention further pertains to analgesic pharmaceutical compositions comprising synergistically effective amounts of a **sodium channel-blocking** compound that specifically binds to the **SS1** or **SS2 subunit** of a **sodium channel** and an opioid analgesic agent.
- SUMM [0009] An object of this invention is to provide a potent analgesic composition containing a long-acting analgesic **sodium channel-blocking** compound that binds to the **SS1** or **SS2 subunit** of a **sodium channel**, and an opioid analgesic agent, with a reduced propensity for causing undesirable adverse effects.
- SUMM [0011] It is further an object of the invention to present a method for producing analgesia induced by opioids or **sodium channel blockers** that binds to the **SS1** or **SS2 subunit** in larger mammals, particularly in humans, whereby undesirable side effects of acute and chronic administration of strong opioids and said **sodium channel blockers** are reduced.
- DETD [0017] The present invention is related to producing analgesia in mammals, in particular in humans, by co-administering synergistically effective amounts of (1) a **sodium channel blocking** compound that specifically binds to the **SS1** or **SS2 subunit** of a **sodium channel**; and (2) an opioid analgesic agent. In such a combination, the opioid agent or a pharmaceutically acceptable derivative or salt thereof, can be administered in a low-analgesic dose, or even in a per se sub-analgesic dose. The composition may contain both, a **sodium channel blocking** compound that specifically binds to the **SS1** or **SS2 subunit** of a **sodium channel** and the opioid agent, together in one dosage form or each in a separate dosage form.
- DETD [0018] Tetrodotoxin and saxitoxin are known to be **sodium channel-blocking** compounds that specifically bind to the **SS1** or **SS2 subunit** of a **sodium channel**.
- CLM What is claimed is:
1. A method of producing analgesia in a mammal experiencing pain, comprising administering to the mammal a synergistically analgesic effective combination of an opioid analgesic agent and a compound that binds to the **SS1** or **SS2 subunit** of a **sodium channel** in a pharmaceutically suitable vehicle.
 3. The method of claim 1, wherein the opioid and the compound that binds to the **SS1** or **SS2 subunit** of a **sodium channel** are

administered together in one single dosage form at synergistically analgesic effective doses.

4. The method of claim 1, wherein the opioid and the compound that binds to the SS1 or SS2 subunit of a **sodium channel** are administered in separate dosage forms at synergistically analgesic effective doses.

6. The method of claim 1, wherein the compound that binds to the SS1 or SS2 subunit of a **sodium channel** is tetrodotoxin or a derivative thereof.

11. The method of claim 6, wherein the **sodium channel** blocking compounds is a composition comprising at least one of tetrodotoxin, anhydrotetrodotoxin, tetrodaminotoxin, methoxytetrodotoxin, ethoxytetrodotoxin, deoxytetrodotoxin or tetrodonic acid.

12. The method of claim 1, wherein the compound that binds to the SS1 or SS2 subunit of a **sodium channel** is saxitoxin or a pharmaceutically acceptable salt thereof.

15. A pharmaceutical composition comprising an opioid and a **sodium channel blocker** that specifically binds to the SS1 or SS2 subunit of a **sodium channel** and a pharmaceutically acceptable carrier.

16. The pharmaceutical composition of claim 15, wherein the **sodium channel** blocker is tetrodotoxin represented by the formula I below: ##STR3##

17. The pharmaceutical composition of claim 15, wherein the **sodium channel** blocker is saxitoxin represented by the formula II below: ##STR4##

20. The pharmaceutical composition of claim 15, wherein the **sodium channel** blocker and the opioid are present in a ratio by weight of from 1:100 to 1:30,000.

PI US 2002198226 A1 20021226

L24 ANSWER 4 OF 9 USPTAFULL on STN

SUMM [0021] The present invention includes methods of producing local anesthesia and analgesia, comprising administering a pharmaceutically acceptable composition of a long-acting **sodium channel blocking** compound, wherein the compound binds to the extracellular mouth of the **sodium channels**, to a subject. Preferred compounds include toxins or analogs thereof that specifically bind to a site formed in part by an extracellular region of the alpha **subunit** of a **sodium channel**. Most preferred compounds comprise the class of toxins and analogs that specifically bind to a site formed by the SS1 and SS2 extracellular regions of the alpha **sub-unit** of a **sodium channel**, wherein such compounds include tetrodotoxin, saxitoxin and analogs thereof.

CLM What is claimed is:

1. A method of producing local analgesia or anesthesia in a nerve tissue region of a mammal experiencing pain caused by damage to or stimulation of a nerve tissue, comprising locally administering to the nerve tissue region of the mammal an anesthesically or analgesically effective dose of a pharmaceutical composition comprising a compound that binds to the SS1 or SS2 subunit of a **sodium channel** and a

pharmaceutically suitable vehicle; wherein the nerve tissue region comprises: (i) the peribulbar nerve and its distribution or a part thereof; (ii) the retrobulbar nerve and its distribution or a part thereof; (iii) the whole or a part of cranial nerve III, IV or V and the distribution thereof; (iv) a ciliary ganglion and the whole or a part of the distribution thereof.

4. The method of claim 1, wherein the compound that binds to the SS1 or SS2 subunit of a **sodium channel** is tetrodotoxin.

13. The method of claim 1, wherein the compound that binds to the SS1 or SS2 subunit of a **sodium channel** is saxitoxin.

PI US 2002161013 A1 20021031

L24 ANSWER 5 OF 9 USPTAFULL on STN

AB The composition of the present invention comprises a **sodium channel blocking** compound which is capable of specifically binding to a site, either on an **SS1** region or an **SS2** region, on an extracellular region of a **sodium channel alpha subunit**, and a pharmaceutically acceptable carrier.

SUMM [0004] As **sodium channel blocking** compounds with high selectivity, tetrodotoxin and saxitoxin specifically bind to a site on an extracellular region, either an **SS1** region or an **SS2** region, of a **sodium channel alpha subunit**. Surprisingly, compounds binding the **SS1** or **SS2** region of a **sodium channel** can produce long-acting and potent analgesia or anesthesia with no severe adverse effects (Dong Q. et al, supra, and Ku B. et al, U.S. patent application No. 09/702,826, filed Nov. 1, 2000, Attorney Docket No. 3519-0106P).

CLM What is claimed is:

1. A composition comprising at least one **sodium channel blocking** compound that specifically binds to a site on an **SS1** region or an **SS2** region of a **sodium channel alpha subunit** and a pharmaceutically acceptable carrier comprising an aqueous solution of a weak organic acid and propylene glycol and having a pH ranging from 3.0 to 5.0.

3. The composition of claim 1 wherein the at least one **sodium channel** blocking compound is tetrodotoxin or an analog thereof.

4. The composition of claim 1 wherein the at least one **sodium channel** blocking compound is saxitoxin or an analog thereof.

15. A composition comprising at least one **sodium channel blocking** compound that specifically binds to a site on an **SS1** region or an **SS2** region of a **sodium channel alpha subunit** and a pharmaceutically acceptable carrier comprising an aqueous solution of a weak organic acid and having a pH ranging from 3.0 to 5.0.

17. The composition of claim 15, wherein the at least one **sodium channel** blocking compound is tetrodotoxin or an analog thereof.

18. The composition of claim 16, wherein the at least one **sodium channel** blocking compound is tetrodotoxin or an analog thereof.

19. A composition comprising at least one **sodium channel blocking** compound that specifically binds to a site on an **SS1** region or an **SS2** region of a

sodium channel alpha subunit and a pharmaceutically acceptable carrier comprising an aqueous solution of a C.sub.2 to C.sub.6 alkane glycol and having a pH ranging from 3.0 to 5.0.

21. The composition of claim 19, wherein the at least one **sodium channel** blocking compound is tetrodotoxin or an analog thereof.

22. The composition of claim 20, wherein the at least one **sodium channel** blocking compound is tetrodotoxin or an analog thereof.

PI US 2002119987 A1 20020829
 US 6559154 B2 20030506

L24 ANSWER 6 OF 9 USPATFULL on STN

SUMM Saxitoxin (STX) is a highly selective and highly active **sodium channel blocking** compound. According to U.S. Pat. No. 6,030,974, both TTX and STX specifically bind to a site on an extracellular region of a **sodium channel alpha subunit**. The site is in either an **SS1** region or an **SS2** region (Evans, Tetrodotoxin, Saxitoxin, and Related Substances: Their Applications in Neurobiology, International Review of Neurobiology, Vol. 15, pp. 83-166, 1972, Academic Press).

CLM What is claimed is:

1. A method for producing analgesia in a mammal experiencing pain comprising systemically administering an amount of a composition comprising a **sodium channel** blocking compound, in a suitable pharmaceutical vehicle, effective to alleviate the pain.
2. The method of claim 1, wherein the **sodium channel** blocking compound is one selected from the group consisting of tetrodotoxin, anhydrotetrodotoxin, tetradaminotoxin, methoxytetrodotoxin, ethoxytetrodotoxin, deoxytetrodotoxin and tetradonic acid.
7. The method of claim 1, wherein the **sodium channel** blocking compound is administered in a dose of 0.1 to 5 µg per kilogram body weight.
9. The method of claim 1, wherein the **sodium channel** blocking compound does not cause drug dependence or addiction in the mammal.
11. The method of claim 1, wherein the **sodium channel** blocking compound does not have any non-reversible adverse effects.
12. The method of claim 1, wherein the **sodium channel** blocking compound does not produce local intramuscular irritation at the region where the systemic administration is performed.
13. The method of claim 1, wherein the **sodium channel** blocking compound does not produce any general hypersensitivity reaction in the mammal.
14. The method of claim 1, wherein the **sodium channel** blocking compound does not induce haemolysis or vascular stimulation in the mammal.
19. The method of claim 1, wherein the **sodium channel** blocking compound comprises a tetrahydropurine moiety comprising two guanidine units fused together in a stable azaketal linkage, having a molecular formula C.sub.10H.sub.17N.sub.7O.sub.4, (mol. wt. 299.30) or a derivative thereof.

L66 ANSWER 3 OF 118 CAPLUS COPYRIGHT 2004 ACS on STN
 AN 1996:612239 CAPLUS
 DN 125:265791
 ED Entered STN: 14 Oct 1996
 TI The $\beta 1$ **sodium channel subunit** modifies
 the interactions of neurotoxins and local anesthetics with the rat brain
 IIA α **sodium channel** in isolated membranes but
 not in intact cells
 AU Bonhaus, Douglas W.; Herman, Ronald C.; Brown, Christine M.; Cao, Zhen;
 Chang, Li-Feng; Loury, Dana N.; Sze, Ping; Zhang, Li; Hunter, John C.
 CS Roche Bioscience, Palo Alto, CA, 94304, USA
 SO Neuropharmacology (1996), 35(5), 605-613
 CODEN: NEPHBW; ISSN: 0028-3908
 PB Elsevier
 DT Journal
 LA English
 CC 1-11 (Pharmacology)
 Section cross-reference(s): 4
 AB Mammalian brain **sodium channels** consist of an α
subunit and two smaller β **subunits**. The role of
 the $\beta 1$ **subunit** in modulating ligand interactions at these
 channels was examined using a cell line stably expressing human $\beta 1$ and
 rat brain IIA α **subunits**. Coexpression of the $\beta 1$
subunit had no effect on the potencies of **sodium**
channel blockers in inhibiting whole cell [3H]batrachotoxinin A
 benzoate([3H]BTX) binding or veratridine-stimulated [14C]
guanidinium influx. Coexpression of the $\beta 1$ **subunit**
 also had no effect on the potencies of α scorpion toxin, brevetoxin,
 or RU 39568 in stimulating [14C]**guanidinium** influx. By
 contrast, coexpression of the $\beta 1$ **subunit** had dramatic
 effects on ligand interactions in isolated membranes. In isolated
 membranes of cells expressing only the α **subunit**, the
 neurotoxins had no stimulatory effect on [3H]BTX binding and the potencies
 of local anesthetic-like channel inhibitors were 10-100-fold lower than
 those at native **sodium channels**. Whereas in membranes
 of cells coexpressing the $\beta 1$ **subunit**, the neurotoxins
 increased [3H]BTX binding 30-fold and the potencies of the **sodium**
channel inhibitors closely matched those found at native
sodium channels. These findings indicate that the
 $\beta 1$ **subunit** is not required for the binding of
sodium channel activators or inhibitors but rather, that
 the $\beta 1$ **subunit** may stabilize the α **subunit**
 in a functional conformation thereby allowing detection of these
 interactions in disrupted membranes.
 ST **sodium channel subunit** neurotoxin anesthetic
 brain
 IT Toxins
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
 (Biological study); PROC (Process)
 (scorpion; $\beta 1$ **sodium channel subunit**
 modifies interactions of neurotoxins and local anesthetics with rat
 brain IIA α **sodium channel** in isolated
 membranes but not in intact cells)
 IT Brain
 ($\beta 1$ **sodium channel subunit** modifies
 interactions of neurotoxins and local anesthetics with rat brain IIA
 α **sodium channel** in isolated membranes but
 not in intact cells)
 IT Anesthetics
 (local, $\beta 1$ **sodium channel subunit**
 modifies interactions of neurotoxins and local anesthetics with rat
 brain IIA α **sodium channel** in isolated
 membranes but not in intact cells)
 IT Toxins

L13 ANSWER 32 OF 48 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
 on STN
 AN 1998034405 EMBASE
 TI A critical role for the S4-S5 intracellular loop in domain IV of
 the sodium channel α -subunit in fast
 inactivation.
 AU McPhee J.C.; Ragsdale D.S.; Scheuer T.; Catterall W.A.
 CS J.C. McPhee, Department of Pharmacology, Box 357280, University of
 Washington, Seattle, WA 98195-7280, United States
 SO Journal of Biological Chemistry, (1998) 273/2 (1121-1129).
 Refs: 49
 ISSN: 0021-9258 CODEN: JBCHA3
 CY United States
 DT Journal; Article
 FS 029 Clinical Biochemistry
 LA English
 SL English
 AB Na⁺ channel fast inactivation is thought to involve the closure of an
 intracellular inactivation gate over the channel pore. Previous studies
 have implicated the intracellular loop connecting domains III and IV and a
 critical IFM motif within it as the inactivation gate, but amino acid
 residues at the intracellular mouth of the pore required for gate closure
 and binding have not been positively identified. The short intracellular
 loops connecting the S4 and S5 segments in each domain of the
 Na⁺ channel α -subunit are good candidates for this role
 in the Na⁺ channel inactivation process. In this study, we used scanning
 mutagenesis to examine the role of the IVS4-S5 region in fast
 inactivation. Mutations F1651A, near the middle of the loop, and L1660A
 and N1662A, near the COOH-terminal end, substantially disrupted Na⁺
 channel fast inactivation. The mutant F1651A conducted Na⁺ currents that
 decayed very slowly, while L1660A and N1662A had large sustained Na⁺
 currents at the end of 30-ms depolarizing pulses. Inactivation of
 macroscopic Na⁺ currents was nearly abolished by the N1662A mutation and
 the combination of the F1651A/L1660A mutations. Single channel analysis
 revealed frequent reopenings for all three mutants during 40-ms
 depolarizing pulses, indicating a substantial impairment of the stability
 of the inactivated state compared with wild type (WT). The F1651A and
 N1662A mutants also had increased mean open times relative to WT,
 indicating a slowed rate of entry into the inactivated state. In addition
 to these effects on inactivation of open Na⁺ channels, mutants F1651A,
 L1660A, and N1662A also impaired fast inactivation of closed Na⁺ channels,
 as assessed from measurements of the maximum open probability of single
 channels. The peptide KIFMK mimics the IFM motif of the inactivation gate
 and provides a test of the effect of mutations on the hydrophobic
 interaction of this motif with the inactivation gate receptor. KIFMK
 restores fast inactivation of open channels to the F1651A/L1660A mutant
 but does not restore fast inactivation of closed F1651A/L1660A channels,
 suggesting that these residues interact with the IFM motif during
 inactivation of closed channels. Our results implicate F1651, L1660, and
 N1662 of the IVS4-S5 loop in inactivation of both closed and
 open Na⁺ channels and suggest that the IFM motif of the inactivation gate
 interacts with F1651 and/or L1660 in the IVS4-S5 loop during
 inactivation of closed channels.
 CT Medical Descriptors:
 *sodium transport
 channel gating
 protein domain
 sodium current
 hydrophobicity
 xenopus laevis
 molecular interaction
 mutagenesis
 nonhuman

rat
animal tissue
animal cell
article
priority journal
Drug Descriptors:

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on STN

AN 1999204613 EMBASE

TI Batrachotoxin-resistant Na⁺ channels derived from point mutations in
transmembrane segment D4-S6.

AU Wang S.-Y.; Ging Kuo Wang

CS Dr. G.K. Wang, Department of Anesthesia, Brigham and Women's Hospital, 75
Francis St., Boston, MA 02115, United States. wang@zeus.bwh.harvard.edu

SO Biophysical Journal, (1999) 76/6 (3141-3149).
Refs: 30
ISSN: 0006-3495 CODEN: BIOJAU

CY United States

DT Journal; Article

FS 022 Human Genetics
029 Clinical Biochemistry

LA English

SL English

AB Local anesthetics (LAs) block voltage-gated Na⁺ channels in excitable
cells, whereas batrachotoxin (BTX) keeps these channels open persistently.
Previous work delimited the LA receptor within the D4-S6 segment
of the Na⁺ channel α - subunit, whereas the putative BTX
receptor was found within the D1-S6. We mutated residues at D4-
S6 critical for LA binding to determine whether such mutations
modulate the BTX phenotype in rat skeletal muscle Na⁺ channels
(μ 1/rSkml). We show that μ 1-F1579K and μ 1-N1584K channels become
completely resistant to 5 μ M BTX. In contrast, μ 1-Y1586K channels
remain BTX-sensitive; their fast and slow inactivation is eliminated by
BTX after repetitive depolarization. Furthermore, we demonstrate that
cocaine elicits a profound time-dependent block after channel activation,
consistent with preferential LA binding to BTX-modified open channels. We
propose that channel opening promotes better exposure of receptor sites
for binding with BTX and LAs, possibly by widening the bordering area
around D1-S6, D4-S6 and the pore region. The BTX
receptor is probably located at the interface of D1- S6 and D4-
S6 segments adjacent to the LA receptor. These two S6
segments may appose too closely to bind BTX and LAs simultaneously when
the channel is in its resting closed state.

CT Medical Descriptors:
*sodium channel
point mutation
channel gating
membrane binding
membrane depolarization
receptor binding
binding site
human
human cell
article
Drug Descriptors:
batrachotoxin

RN (batrachotoxin) 23509-16-2

L13 ANSWER 19 OF 48 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
 on STN
 AN 2000157853 EMBASE
 TI Potent blockade of **sodium channels** and protection of
 brain tissue from ischemia by BIII 890 CL.
 AU Carter A.J.; Grauert M.; Pschorn U.; Bechtel W.D.; Bartmann-Lindholm C.;
 Qu Y.; Scheuer T.; Catterall W.A.; Weiser T.
 CS A.J. Carter, Dept. of Centr. Nervous System Res., Boehringer Ingelheim
 Pharma KG, 55216 Ingelheim am Rhein, Germany.
 carter@ing.boehringer-ingelheim.com
 SO Proceedings of the National Academy of Sciences of the United States of
 America, (25 Apr 2000) 97/9 (4944-4949).
 Refs: 43
 ISSN: 0027-8424 CODEN: PNASA6
 CY United States
 DT Journal; Article
 FS 008 Neurology and Neurosurgery
 030 Pharmacology
 037 Drug Literature Index
 LA English
 SL English
 AB We have synthesized a new benzomorphan derivative,
 2R[2 α ,3(S*),6 α]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-3-[2-
 (phenylmethoxy)propyl]-2,6-methano-3-benzazocin-10-ol hydrochloride (BIII
 890 CL), which displaced [3H]batrachotoxinin A-20 α -benzoate from
neurotoxin receptor site 2 of the Na⁺ channel in rat brain synaptosomes
 (IC₅₀ = 49 nM), but exhibited only low affinity for 65 other receptors and
 ion channels. BIII 890 CL inhibited Na⁺ channels in cells transfected with
 type IIA Na⁺ channel α **subunits** and shifted steady-state
 inactivation curves to more negative potentials. The IC₅₀ value for the
 inactivated Na⁺ channel was much lower (77 nM) than for Na⁺ channels in
 the resting state (18 μ M). Point mutations E1764A and Y1771A in
transmembrane segment S6 in domain IV of the α
subunit reduced the voltage- and frequency-dependent block,
 findings which suggest that BIII 890 CL binds to the local anesthetic
 receptor site in the pore. BIII 890 CL inhibited veratridine-induced
 glutamate release in brain slices, as well as glutamate release and
 neurotoxicity in cultured cortical neurons. BIII 890 CL (3-30 mg/kg s.c.)
 reduced lesion size in mice and rats when administered 5 min after
 permanent focal cerebral ischemia at doses that did not impair motor
 coordination. In contrast to many other agents, BIII 890 CL was
 neuroprotective in both cortical and subcortical regions of the rat brain.
 Our results demonstrate that BIII 890 CL is a potent, selective, and
 highly use-dependent Na⁺ channel blocker that protects brain tissue from
 the deleterious effects of focal cerebral ischemia in rodents.
 CT Medical Descriptors:
 ***sodium channel**
 *brain protection
 *brain ischemia: DT, drug therapy
 *brain ischemia: PC, prevention
 drug potency
 drug synthesis
 brain synaptosome
 receptor affinity
 point mutation
 protein domain
 drug receptor binding
 brain slice
 neurotoxicity: DT, drug therapy
 neurotoxicity: PC, prevention
 brain nerve cell
 drug selectivity
 neuroprotection

nonhuman
male
mouse
rat
animal experiment
animal model
controlled study
animal tissue
animal cell
article
priority journal

Drug Descriptors:

*sodium ion: EC, endogenous compound
*benzomorphan derivative: DV, drug development
*benzomorphan derivative: DT, drug therapy
*benzomorphan derivative: PD, pharmacology
*benzomorphan derivative: SC, subcutaneous drug administration
*1,2,3,4,5,6 hexahydro 6,11,11 trimethyl 3 [2 (phenylmethoxy)propyl] 2,6
methano 3 benzazocin 10 ol: DV, drug development
*1,2,3,4,5,6 hexahydro 6,11,11 trimethyl 3 [2 (phenylmethoxy)propyl] 2,6
methano 3 benzazocin 10 ol: DT, drug therapy
*1,2,3,4,5,6 hexahydro 6,11,11 trimethyl 3 [2 (phenylmethoxy)propyl] 2,6
methano 3 benzazocin 10 ol: PD, pharmacology
*1,2,3,4,5,6 hexahydro 6,11,11 trimethyl 3 [2 (phenylmethoxy)propyl] 2,6
methano 3 benzazocin 10 ol: SC, subcutaneous drug administration
*sodium channel blocking agent: DV, drug development
*sodium channel blocking agent: DT, drug therapy
*sodium channel blocking agent: PD, pharmacology
*sodium channel blocking agent: SC, subcutaneous drug

administration

batrachotoxinin A 20alpha benzoate
veratridine
glutamic acid: EC, endogenous compound
local anesthetic agent
unclassified drug
biii 890 cl

RN (sodium ion) 17341-25-2; (batrachotoxinin A 20alpha benzoate) 78870-19-6;
(veratridine) 71-62-5; (glutamic acid) 11070-68-1, 138-15-8, 56-86-0,
6899-05-4

CN (1) Biii 890 cl

CO (1) Boehringer Ingelheim (Germ

L13 ANSWER 17 OF 48 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
 on STN
 AN 2000314670 EMBASE
 TI Residues in Na⁺ channel D3-S6 segment modulate both
 batrachotoxin and local anesthetic affinities.
 AU Wang S.-Y.; Nau C.; Ging Kuo Wang
 CS Dr. G.K. Wang, Department of Anesthesia, Brigham and Women's Hospital, 75
 Francis St., Boston, MA 02115, United States. wang@zeus.bwh.harvard.edu
 SO Biophysical Journal, (2000) 79/3 (1379-1387).
 Refs: 40
 ISSN: 0006-3495 CODEN: BIOJAU
 CY United States
 DT Journal; Article
 FS 002 Physiology
 029 Clinical Biochemistry
 037 Drug Literature Index
 LA English
 SL English
 AB Batrachotoxin (BTX) alters the gating of voltage-gated Na⁺ channels and
 causes these channels to open persistently, whereas local anesthetics
 (LAs) block Na⁺ conductance. The BTX and LA receptors have been mapped to
 several common residues in D1-S6 and D4-S6 segments of
 the Na⁺ channel α - subunit. We substituted individual
 residues with lysine in homologous segment D3-S6 of the rat
 muscle μ 1 Na⁺ channel from F1274 to N1281 to determine whether
 additional residues are involved in BTX and LA binding. Two mutant
 channels, μ 1-S1276K and μ 1-L1280K, when expressed in mammalian
 cells, become completely resistant to 5 μ M BTX during repetitive
 pulses. The activation and/or fast inactivation gating of these mutants is
 substantially different from that of wild type. These mutants also display
 .apprx.10-20-fold reduction in bupivacaine affinity toward their
 inactivated state but show only approximately twofold affinity changes
 toward their resting state. These results demonstrate that residues
 μ 1-S1276 and μ 1-L1280 in D3-S6 are critical for both BTX
 and LA binding interactions. We propose that LAs interact readily with
 these residues from D3-S6 along with those from D1-S6
 and D4-S6 in close proximity when the Na⁺ channel is in its
 inactivated state. Implications of this state-dependent binding model for
 the S6 alignment are discussed.
 CT Medical Descriptors:
 *sodium channel
 *channel gating
 sodium conductance
 drug receptor binding
 mammal cell
 membrane potential
 sequence analysis
 nonhuman
 rat
 animal cell
 article
 Drug Descriptors:
 *batrachotoxin
 *local anesthetic agent: PD, pharmacology
 bupivacaine
 RN (batrachotoxin) 23509-16-2; (bupivacaine) 18010-40-7, 2180-92-9,
 55750-21-5

L13 ANSWER 15 OF 48 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

AN 2001022308 EMBASE

TI Molecular determinants of voltage-dependent gating and binding of
pore-blocking drugs in transmembrane segment IIIS6 of the Na(+) channel
 α subunit.

AU Yarov-Yarovoy V.; Brown J.; Sharp E.M.; Clare J.J.; Scheuer T.; Catterall
W.A.

CS W.A. Catterall, Dept. of Pharmacology, University of Washington, Mail Stop
357280, Seattle, WA 98195-7280, United States. wcatt@u.washington.edu

SO Journal of Biological Chemistry, (5 Jan 2001) 276/1 (20-27).
Refs: 47
ISSN: 0021-9258 CODEN: JBCHA3

CY United States

DT Journal; Article

FS 029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index

LA English

SL English

AB Mutations of amino acid residues in the inner two-thirds of the S6
segment in domain III of the rat brain type IIA Na(+) channel (G1460A to
I1473A) caused periodic positive and negative shifts in the voltage
dependence of activation, consistent with an α -helix having one face
on which mutations to alanine oppose activation. Mutations in the outer
one-third of the IIIS6 segment all favored activation. Mutations in the
inner half of IIIS6 had strong effects on the voltage dependence of
inactivation from closed states without effect on open-state inactivation.
Only three mutations had strong effects on block by local anesthetics and
anticonvulsants. Mutations L1465A and I1469A decreased affinity of
inactivated Na(+) channels up to 8-fold for the anticonvulsant lamotrigine
and its congeners 227c89, 4030w92, and 619c89 as well as for the local
anesthetic etidocaine. N1466A decreased affinity of inactivated Na(+) channels
for the anticonvulsant 4030w92 and etidocaine by 3- and 8-fold,
respectively, but had no effect on affinity of the other tested compounds.
Leu-1465, Asn-1466, and Ile-1469 are located on one side of the IIIS6
helix, and mutation of each caused a positive shift in the voltage
dependence of activation. Evidently, these amino acid residues face the
lumen of the pore, contribute to formation of the high-affinity receptor
site for pore-blocking drugs, and are involved in voltage-dependent
activation and coupling to closed-state inactivation.

CT Medical Descriptors:
*sodium channel
*drug binding site
ion channel
action potential
gene mutation
gene expression
oocyte
Xenopus
voltage clamp
nonhuman
animal cell
article
priority journal
Drug Descriptors:
*anticonvulsive agent: CM, drug comparison
*anticonvulsive agent: PD, pharmacology
*lamotrigine: CM, drug comparison
*lamotrigine: PD, pharmacology
*local anesthetic agent: CM, drug comparison
*local anesthetic agent: PD, pharmacology
*etidocaine: CM, drug comparison

*etidocaine: PD, pharmacology
*sipatrigine: CM, drug comparison
*sipatrigine: PD, pharmacology
sodium ion

RN (lamotrigine) 84057-84-1; (etidocaine) 36637-18-0, 36637-19-1;
(sipatrigine) 130800-90-7; (sodium ion) 17341-25-2
CN (1) 619c89
CO (1) Glaxo Wellcome

L13 ANSWER 14 OF 48 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
 on STN
 AN 2001104701 EMBASE
 TI Single point mutations affect fatty acid block of human myocardial
sodium channel α subunit Na(+) channels.
 AU Xiao Y.-F.; Ke Q.; Wang S.-Y.; Auktor K.; Yang Y.; Ging Kuo Wang; Morgan
 J.P.; Leaf A.
 CS A. Leaf, Massachusetts General Hospital, Building 149, 13th Street,
 Charlestown, MA 02129, United States. aleaf@partners.org
 SO Proceedings of the National Academy of Sciences of the United States of
 America, (13 Mar 2001) 98/6 (3606-3611).
 Refs: 25
 ISSN: 0027-8424 CODEN: PNASA6
 CY United States
 DT Journal; Article
 FS 029 Clinical Biochemistry
 LA English
 SL English
 AB Suppression of cardiac voltage-gated Na(+) currents is probably one of the
 important factors for the cardioprotective effects of the n-3
 polyunsaturated fatty acids (PUFAs) against lethal arrhythmias. The
 α subunit of the human cardiac Na(+) channel (hH1 α)
 and its mutants were expressed in human embryonic kidney (HEK293t) cells.
 The effects of single amino acid point mutations on fatty acid-induced
 inhibition of the hH1 α Na(+) current (I(Na)) were assessed.
 Eicosapentaenoic acid (EPA, C20:5n-3) significantly reduced I(Na) in
 HEK293t cells expressing the wild type, Y1767K, and F1760K of hH1 α
 Na(+) channels. The inhibition was voltage and concentration-dependent
 with a significant hyperpolarizing shift of the steady state of I(Na). In
 contrast, the mutant N406K was significantly less sensitive to the
 inhibitory effect of EPA. The values of the shift at 1, 5, and 10 μ M
 EPA were significantly smaller for N406K than for the wild type.
 Coexpression of the β (1) **subunit** and N406K further
 decreased the inhibitory effects of EPA on I(Na) in HEK293t cells. In
 addition, EPA produced a smaller hyperpolarizing shift of the V(1/2) of
 the steady-state inactivation in HEK293t cells coexpressing the β (1)
subunit and N406K. These results demonstrate that substitution of
 asparagine with lysine at the site of 406 in the domain-1-segment-6 region
 (D1-S6) significantly decreased the inhibitory effect of PUFAs
 on I(Na), and coexpression with β (1) decreased this effect even more.
 Therefore, asparagine at the 406 site in hH1 α may be important for
 the inhibition by the PUFAs of cardiac voltage-gated Na(+) currents, which
 play a significant role in the antiarrhythmic actions of PUFAs.
 CT Medical Descriptors:
 *heart protection
 *point mutation
 metabolic inhibition
 sodium current
sodium channel
 protein expression
 alpha chain
 article
 priority journal
 Drug Descriptors:
 *polyunsaturated fatty acid
 icosapentaenoic acid
 RN (icosapentaenoic acid) 25378-27-2, 32839-30-8

L36 ANSWER 46 OF 254 CAPLUS COPYRIGHT 2004 ACS on STN
AB Intracerebroventricular (i.c.v.) administration of 75 µg KCl or 0.5 µg pertussis toxin to mice reduced the antinociceptive activity of several opioids in the tail-flick test. The analgesia from morphine, etorphine, morphiceptin and human β-endorphin was slightly decreased by KCl. The **toxin** reduced the **analgesic** effect of the **opioids** to a greater extent. KCl and pertussis **toxin** abolished the activity of DAME, DADLE, DPDPE, DAGO, and proenkephalin-derived peptides to a much greater extent. KCl-sensitive **opioids** administered a few min before KCl protected the DADLE-induced analgesia from the abolishing effect of KCl. KCl-resistant opioids were much weaker in producing this protection. The **opioid** antagonists naloxone and naltrexone also protected the DADLE **analgesic** activity. Thus, KCl treatment altered the **opioid** receptor function in a manner similar to that of pertussis **toxin**.

IT **Analgesics**

(**opioids** as, pertussis **toxin** and potassium
antagonism of)

ACCESSION NUMBER: 1989:587361 CAPLUS
DOCUMENT NUMBER: 111:187361
TITLE: Protection against the abolishing effect of icv
potassium chloride upon opioid analgesia in mice: a
comparative study with pertussis toxin
AUTHOR(S): Garzon, J.; Sanchez-Blazquez, P.
CORPORATE SOURCE: Cajal Inst., CSIC, Madrid, 28006, Spain
SOURCE: Advances in the Biosciences (Oxford) (1989), 75(Prog.
Opioid Res.), 507-10
CODEN: AVBIB9; ISSN: 0065-3446
DOCUMENT TYPE: Journal
LANGUAGE: English

L36 ANSWER 52 OF 254 CAPLUS COPYRIGHT 2004 ACS on STN

AB Neurotoxin of cobra (*Naja naja*) venom, given intracerebroventricularly to rats, induced analgesia; the **analgesic** action was not affected by reserpine, slightly antagonized by naloxone, and completely blocked by atropine. The **neurotoxin** also had an **analgesic** effect in morphine-tolerant rats. Apparently, the **analgesic** mechanism of cobra **neurotoxin** is related to the central muscarinic system, but not to brain monoamines or the **opioidergic** system.

IT Nervous system

(central, **opioidergic**, **neurotoxin** of cobra venom
analgesic effect in relation to)

ACCESSION NUMBER: 1988:143329 CAPLUS

DOCUMENT NUMBER: 108:143329

TITLE: Mechanisms of the analgesic action of the neurotoxin of cobra venom

AUTHOR(S): Chen, Ruzhu; Wu, Xiurong

CORPORATE SOURCE: Dep. Pharmacol., Sun Yatsen Univ. Med. Sci.,
Guangzhou, 510037, Peop. Rep. China

SOURCE: Zhongguo Yaolixue Yu Dulixue Zazhi (1988), 2(1), 1-5
CODEN: ZYYZEW; ISSN: 1000-3002

DOCUMENT TYPE: Journal

LANGUAGE: Chinese